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RESEARCH ARTICLE

Heart failure, chronic obstructive pulmonary disease and efficacy and safety of dapagliflozin in heart failure with mildly reduced or preserved ejection fraction: Insights from DELIVER

**Jawad H. Butt[1,2], Henri Lu[3], Toru Kondo[1,4], Erasmus Bachus[5], Rudolf A. de Boer[6], Silvio E. Inzucchi[7], Pardeep S. Jhund[1], Mikhail N. Kosiborod[8], Carolyn S.P. Lam[9], Felipe A. Martinez[10], Muthiah Vaduganathan[3], Scott D. Solomon[3], and John J.V. McMurray[1]*

[1]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [2]Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; [3]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [4]Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [5]Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, Gothenburg, Sweden; [6]Erasmus Medical Center, Rotterdam, The Netherlands; [7]Yale School of Medicine, New Haven, CT, USA; [8]Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; [9]National Heart Centre Singapore, Duke-National University of Singapore, Singapore, Singapore; and [10]University of Cordoba, Cordoba, Argentina

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Aim

Chronic obstructive pulmonary disease (COPD) is common in heart failure with a mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) and is associated with worse outcomes. In a pre-specified analysis of DELIVER, we investigated the relationship between COPD status and outcomes, and the efficacy and safety of dapagliflozin, compared with placebo, according to COPD status.

Methods and results

Patients with severe pulmonary disease (including COPD) were excluded from the trial. The primary outcome was a composite of cardiovascular death or worsening heart failure. Of the 6261 patients with data on baseline COPD status, 694 (11.1%) had a known history of this condition. The risk of the primary endpoint was higher in patients with mild-to-moderate COPD compared with those without COPD (adjusted hazard ratio [HR] 1.28, 95% confidence interval [CI] 1.08–1.51). The benefit of dapagliflozin on the primary outcome was consistent irrespective of COPD status (no COPD: HR 0.82 [95% CI 0.72–0.93]; COPD: HR 0.82 [95% CI 0.62–1.10]; $p_{interaction} = 0.98$). Consistent effects were observed for heart failure, cardiovascular, and all-cause hospitalization, and deaths, and composites of these. Dapagliflozin, as compared with placebo, improved the Kansas City Cardiomyopathy Questionnaire scores from baseline to 8 months to a similar extent in patients with and without mild-to-moderate COPD ($p_{interaction} \geq 0.63$). Adverse events and treatment discontinuation were not more frequent with dapagliflozin than with placebo irrespective of COPD status.

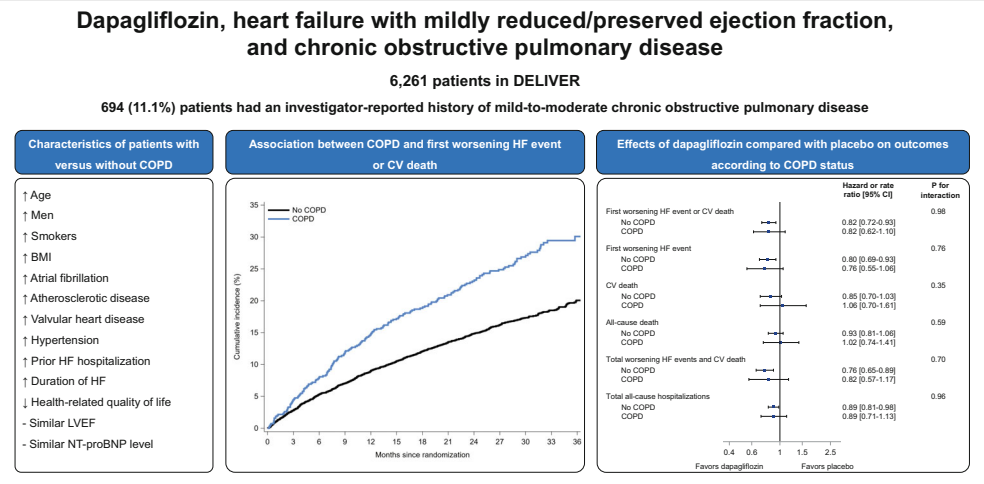
Conclusions

Mild-to-moderate COPD is common in patients with HFmrEF/HFpEF and is associated with worse outcomes. The beneficial effects of dapagliflozin compared with placebo on clinical events and symptoms were consistent, regardless of COPD status.

Clinical Trial Registration: ClinicalTrials.gov NCT03619213.

*Corresponding author. British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK. Tel: +44 141 3303479, Fax: +44 141 3306955, Email: john.mcmurray@glasgow.ac.uk

Graphical Abstract



In a pre-specified analysis of DELIVER, dapagliflozin, compared with placebo, reduced the risk of cardiovascular (CV) death or worsening heart failure (HF) events (and deaths and hospital admissions from any cause), and improved symptoms and health-related quality of life, to a similar extent in patients with and without chronic obstructive pulmonary disease (COPD). In addition, dapagliflozin was safe and well-tolerated, irrespective of COPD status. BMI, body mass index; CI, confidence interval; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Heart failure • Chronic obstructive pulmonary disease • Dapagliflozin • Clinical trial • Outcomes

Introduction

The coexistence of heart failure (HF) with a mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) and chronic obstructive pulmonary disease (COPD) is common.[1–6] In addition, this comorbid intersection results in a worse prognosis than when either condition is present alone.[1–6] Therefore, there is a need for effective therapies in these high-risk individuals with both HFmrEF/HFpEF and COPD.

In the Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial, the sodium–glucose cotransporter 2 (SGLT2) inhibitor, dapagliflozin, compared with placebo, reduced the risk of a worsening HF event or cardiovascular death, and improved symptoms, in 6263 patients with HFmrEF/HFpEF.[7] DELIVER enrolled a larger and broader HFmrEF/HFpEF population, including patients with improved left ventricular ejection fraction, and some with very recent hospitalization, than any prior trial. In this pre-specified analysis, we compared clinical outcomes, including all-cause hospitalization, between patients with and without a history of COPD at randomization. In addition, we examined the causes of death and hospitalizations in these two groups of patients. We also examined the efficacy and safety of dapagliflozin compared with placebo according to whether or not patients had a history of COPD.

Methods

DELIVER was a randomized, double-blind, controlled trial in patients with HFmrEF/HFpEF, examining the efficacy and safety of dapagliflozin 10 mg once daily compared with matching placebo. The design, baseline characteristics, and primary results of DELIVER are published.[7–9] The trial protocol was approved by the ethics committee at all participating institutions, and all patients provided written informed consent.

Study patients

Key inclusion criteria were age ≥40 years, a diagnosis of HF for ≥6 weeks and at least intermittent use of a diuretic, New York Heart Association (NYHA) functional class II–IV, LVEF >40%, evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy), and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥300 pg/ml (≥600 pg/ml if atrial fibrillation on the electrocardiogram at enrolment). Both ambulatory and hospitalized patients were eligible for enrolment. Key exclusion criteria were type 1 diabetes, estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 (calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation), and systolic blood pressure <95 mmHg. In addition, patients with primary pulmonary hypertension, chronic pulmonary embolism, or severe pulmonary disease including COPD (i.e. requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalization

for exacerbation of COPD requiring ventilatory assistance within 12 months prior to enrolment) were excluded. A complete list of exclusion criteria is provided in the design paper.[8]

History of chronic obstructive disease

Data on medical history, including COPD, were investigator-reported and retrieved from the trial electronic case report forms. In a sensitivity analysis, the definition of COPD was expanded to include asthma.

Trial outcomes

The primary outcome in DELIVER was the composite of worsening HF (HF hospitalization or urgent HF visit) or cardiovascular death. The secondary outcomes were total HF events (first and repeat HF events) and cardiovascular death; change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (KCCQ-TSS); death from cardiovascular causes; and death from any cause. In the present analysis, we also examined worsening HF and HF hospitalization; total (first and repeat) cause-specific hospitalizations (investigator-reported and classified according to Medical Dictionary for Regulatory Activities System Organ Classes terms); cause of death; and change from baseline to 8 months in the KCCQ overall and clinical summary score (KCCQ-OSS and -CSS, respectively). Worsening HF events and cause of death were adjudicated by an independent clinical events committee.

Pre-specified safety analyses included serious adverse events, adverse events leading to discontinuation of trial treatment, and selected adverse events, including volume depletion, renal adverse events, amputation, major hypoglycaemia, and diabetic ketoacidosis for consistency across reporting in trials. Safety analyses were only performed in patients who had undergone enrolment and received at least one dose of either dapagliflozin or placebo.

Statistical analyses

Baseline characteristics according to COPD status were summarized as frequencies with percentages, means with standard deviation, or medians with interquartile ranges. Differences in baseline characteristics were tested using the chi-square test for binary or categorical variables and the Wilcoxon test and two-sample *t*-test for non-normal and normally distributed continuous variables, respectively.

Time-to-event data were evaluated using Cox proportional-hazards models, stratified according to type 2 diabetes status and adjusted for treatment assignment, and hazard ratios (HR) with 95% confidence intervals (CIs) were reported. Total events were evaluated with semiparametric proportional-rates models,[10] stratified according to type 2 diabetes status and adjusted for treatment assignment, and rate ratios (RR) with 95% CIs were reported. In addition, HRs and RRs, stratified according to type 2 diabetes status and adjusted for treatment assignment, age, sex, geographical region, systolic blood pressure, heart rate, body mass index, log of NT-proBNP, eGFR, HF duration, a history of HF hospitalization, LVEF, NYHA functional class, a history of coronary artery disease, atrial fibrillation, and smoking status were reported.

To compare the effects of dapagliflozin versus placebo on clinical outcomes, time-to-event data and total events were evaluated with Cox proportional-hazards models and semiparametric proportional-rates models, respectively, and these models were stratified according to type 2 diabetes status. The difference between treatment groups in the change in KCCQ scores from baseline to 8 months was analysed using mixed-effect models for repeated measurements, adjusted for baseline value, visit (month 1, 4 and 8), treatment assignment, and interaction of treatment and visit. The least-squares mean differences with 95% CI between treatment groups were reported.

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and STATA version 17.0 (Stata Corp., College Station, TX, USA).

Results

Of the 6263 patients randomized in DELIVER, two were excluded due to missing history related to COPD. A total of 694 patients (11.1%) had a history of COPD at baseline. The prevalence in men was 12.9% compared with 8.7% in women.

Patient characteristics

Patients with COPD were older, more often men, and more likely to be current smokers and have a higher body mass index than patients without COPD (*Table 1*). They were also more likely to have a history of atrial fibrillation, atherosclerotic disease, valvular heart disease, and hypertension. Although patients with and without COPD had a similar LVEF and NT-proBNP distribution, the former had a longer duration of HF, worse NYHA functional class and KCCQ scores, and a higher rate of prior HF hospitalization.

Regarding pharmacological therapy, patients with COPD were more frequently treated with a loop diuretic and anticoagulant, but less often with an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. The proportion of patients treated with a beta-blocker was similar in the two groups, although patients with COPD were more likely to be treated with nebivolol (a beta-1-selective receptor antagonist), and less often with carvedilol (non-selective), compared to those without COPD.

Among patients with COPD, 28.2% were treated with a long-acting beta-2-adrenoreceptor agonist (19.6% with a short-acting agent in this class), 28.0% with a muscarinic antagonist, 23.8% with an inhaled corticosteroid, 4.3% with a xanthine derivative (e.g. theophylline), and 3.2% with a leukotriene receptor antagonist.

Outcomes according to a history of COPD

Patients with COPD had a higher unadjusted risk of the primary composite outcome, along with cardiovascular and all-cause death, as well as cardiovascular and all-cause hospitalization (both first events and total hospitalizations) compared to individuals without COPD (*Table 2* and online supplementary *Table S1*). The rate (95% CI) of the primary outcome (cardiovascular death or a worsening HF event) was 8.1 (7.6–8.7) among participants without COPD compared to 13.3 (11.6–15.4) per 100 person-years in those with COPD (*Table 2*). The risk of all outcomes was attenuated after adjustment for other prognostic variables.

The most commonly adjudicated cause of death was ascribed to cardiovascular causes, mainly sudden death and death due to worsening HF. While the proportion of sudden deaths was

Table 1 Baseline characteristics according to a history of chronic obstructive pulmonary disease

	No COPD ($n = 5567$)	COPD ($n = 694$)	p-value
Age (years), mean (SD)	71.6 ± 9.7	72.2 ± 8.5	0.091
Age (years), *n* (%)			0.025
≤65	1364 (24.5)	139 (20.0)	
66–75	2122 (38.1)	290 (41.8)	
≥76	2081 (37.4)	265 (38.2)	
Sex, *n* (%)			<0.001
Women	2507 (45.0)	240 (34.6)	
Men	3060 (55.0)	454 (65.4)	
Race, *n* (%)			<0.001
White	3854 (69.2)	583 (84.0)	
Black or African American	136 (2.4)	23 (3.3)	
Asian	1196 (21.5)	78 (11.2)	
Other	381 (6.8)	10 (1.4)	
Geographic region, *n* (%)			<0.001
Europe and Saudi Arabia	2615 (47.0)	388 (55.9)	
Asia	1152 (20.7)	74 (10.7)	
Latin America	1127 (20.2)	54 (7.8)	
North America	673 (12.1)	178 (25.6)	
Physiological measures			
Systolic blood pressure (mmHg), mean (SD)	128.4 ± 15.4	126.8 ± 15.1	0.009
Heart rate (bpm), mean (SD)	71.4 ± 11.8	71.8 ± 11.4	0.45
Body mass index (kg/m^2), mean (SD)	29.8 ± 6.1	30.6 ± 6.3	0.001
NT-proBNP (pg/ml), median (IQR)			
No atrial fibrillation/flutter on baseline ECG	714 (468–1252)	732 (479–1516)	0.13
Atrial fibrillation/flutter on baseline ECG	1398 (957–2210)	1433 (987–2212)	0.68
HbA1c (%), mean (SD)	6.6 ± 1.4	6.6 ± 1.3	0.82
Creatinine (μmol/L), mean (SD)	102.0 ± 31.0	106.1 ± 31.3	0.001
eGFR[a] (ml/min/1.73 m^2), mean (SD)	61.2 ± 19.2	59.8 ± 18.5	0.081
eGFR[a] (ml/min/1.73 m^2), *n* (%)			0.39
<60	2718 (48.8)	351 (50.6)	
≥60	2848 (51.2)	343 (49.4)	
Smoking status, *n* (%)			<0.001
Current	362 (6.5)	122 (17.6)	
Former	1885 (33.9)	375 (54.0)	
Never	3320 (59.6)	197 (28.4)	
Duration of HF, *n* (%)			0.001
0–3 months	511 (9.2)	57 (8.2)	
>3–6 months	540 (9.7)	52 (7.5)	
>6–12 months	768 (13.8)	72 (10.4)	
>1–2 years	896 (16.1)	99 (14.3)	
>2–5 years	1379 (24.8)	190 (27.4)	
>5 years	1468 (26.4)	224 (32.3)	
LVEF (%), mean (SD)	54.2 ± 8.8	53.9 ± 8.5	0.36
LVEF (%), *n* (%)			0.49
≤49	1874 (33.7)	242 (34.9)	
50–59	1999 (35.9)	256 (36.9)	
≥60	1694 (30.4)	196 (28.2)	
NYHA class, *n* (%)			<0.001
II	4258 (76.5)[b]	454 (65.4)	
III	1292 (23.2)	239 (34.4)	
IV	17 (0.3)	1 (0.1)	
KCCQ-TSS, mean (SD)	70.6 ± 22.2	65.3 ± 21.5	<0.001
KCCQ-CSS, mean (SD)	68.9 ± 20.7	63.6 ± 19.8	<0.001
KCCQ-OSS, mean (SD)	67.2 ± 20.3	62.6 ± 19.6	<0.001

Table 1 (Continued)

	No COPD ($n = 5567$)	COPD ($n = 694$)	p-value
Medical history, *n* (%)			
Hospitalization for HF	2186 (39.3)	352 (50.7)	<0.001
Atrial fibrillation/flutter	3101 (55.7)	451 (65.0)	<0.001
Stroke	527 (9.5)	70 (10.1)	0.60
Angina	1299 (23.3)	198 (28.5)	0.002
Myocardial infarction	1439 (25.8)	200 (28.8)	0.093
Any coronary artery disease	2772 (49.8)	392 (56.5)	<0.001
Any atherosclerotic disease	3108 (55.8)	444 (64.0)	<0.001
Valvular heart disease	1446 (26.0)	219 (31.6)	0.002
Hypertension	4920 (88.4)	631 (90.9)	0.046
Type 2 diabetes mellitus	2483 (44.6)	323 (46.5)	0.33
Treatment, *n* (%)			
Loop diuretic	4220 (75.8)	589 (84.9)	<0.001
Other diuretic (excluding loop and MRA)	1202 (21.6)	141 (20.3)	0.44
ACEi/ARB	4060 (73.0)	481 (69.3)	0.042
ARNI	274 (4.9)	27 (3.9)	0.23
Beta-blocker	4604 (82.7)	572 (82.4)	0.84
Beta-1 selective beta-blocker	3727 (66.9)	481 (69.3)	0.21
Atenolol	141 (2.5)	7 (1.0)	0.013
Bisoprolol	2044 (36.7)	276 (39.8)	0.12
Metoprolol	1211 (21.8)	143 (20.6)	0.49
Nebivolol	256 (4.6)	53 (7.6)	<0.001
Non-selective beta-blocker and alpha-blocker	817 (14.7)	82 (11.8)	0.043
Carvedilol	810 (14.6)	80 (11.5)	0.032
Other non-selective beta-blocker	81 (1.5)	11 (1.6)	0.79
MRA	2393 (43.0)	273 (39.3)	0.066
Digoxin	264 (4.7)	32 (4.6)	0.88
Lipid-lowering medication	3700 (66.5)	457 (65.9)	0.74
Antiplatelet	2360 (42.4)	270 (38.9)	0.078
Anticoagulant	2946 (52.9)	436 (62.8)	<0.001
Pacemaker	578 (10.4)	84 (12.1)	0.16
CRT-P/CRT-D	86 (1.5)	14 (2.0)	0.35
ICD/CRT-D	143 (2.6)	25 (3.6)	0.11

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; CSS, clinical summary score; eGFR, estimated glomerular filtration rate; Hb1Ac, glycated haemoglobin; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; SD, standard deviation; TSS, total symptom score.

[a]Estimated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation.

[b]One additional patient was NYHA class I.

similar in patients with and without COPD, more patients in the COPD group had a death attributed to worsening HF compared to the non-COPD group (*Figure 1*). Infection was the second most common cause of death, and the proportion of deaths attributed to infection was lower in patients with COPD compared to patients without COPD. The cause of death was undetermined in less than 14% of cases, and this proportion was slightly lower in patients with COPD (*Figure 1*).

Although infections were the second most frequent cause of investigator-reported hospitalization overall, the risk of these was not significantly higher in patients with COPD compared to those without (*Table 2* and *Figure 2*). The rate of hospitalizations for respiratory/thoracic causes was higher in patients with COPD but these admissions were not as frequent as those for cardiovascular causes or even HF alone (*Table 2*). Cancer admissions were even less common and not significantly higher among patients with COPD compared to those without COPD.

The total burden of fatal and non-fatal events was high, reflected in both high mortality rates and the occurrence of repeat hospital admissions; events not related to HF added substantially to this burden. The rate (95% CI) of the pre-specified secondary outcome of cardiovascular deaths and total (first and repeat) HF hospitalizations was 20.4 (18.3–22.8) in patients with COPD compared to 12.7 (12.1–13.3) per 100 person-years in participants without COPD. By contrast, the rate (95% CI) of the broadest composite outcome (all-cause death and total hospitalizations for any cause)

Table 2 Outcomes according to a history of chronic obstructive pulmonary disease

	No COPD ($n = 5567$)	COPD ($n = 694$)
Primary and secondary outcomes		
Primary composite outcome		
No. of events (%)	936 (16.8)	185 (26.7)
Event rate per 100 person-years (95% CI)	8.1 (7.6–8.7)	13.3 (11.6–15.4)
HR (95% CI)[a]	Reference	1.63 (1.39–1.91)
HR (95% CI)[b]	Reference	1.28 (1.08–1.51)
Cardiovascular deaths and worsening HF events (total)		
No. of events	1559	312
Event rate per 100 person-years (95% CI)	12.7 (12.1–13.3)	20.4 (18.3–22.8)
RR (95% CI)[a]	Reference	1.59 (1.31–1.94)
RR (95% CI)[b]	Reference	1.19 (0.98–1.45)
Hospitalization		
HF hospitalizations (total)		
No. of events	1006	209
Event rate per 100 person-years (95% CI)	8.2 (7.7–8.7)	13.7 (11.9–15.7)
RR (95% CI)[a]	Reference	1.66 (1.30–2.11)
RR (95% CI)[b]	Reference	1.18 (0.93–1.50)
Cardiovascular hospitalizations (total)		
No. of events	1660	326
Event rate per 100 person-years (95% CI)	13.5 (12.8–14.1)	21.3 (19.1–23.7)
RR (95% CI)[a]	Reference	1.57 (1.30–1.89)
RR (95% CI)[b]	Reference	1.24 (1.03–1.48)
Infection-related hospitalizations (total)		
No. of events	919	140
Event rate per 100 person-years (95% CI)	7.5 (7.0–8.0)	9.1 (7.7–10.8)
RR (95% CI)[a]	Reference	1.21 (0.99–1.49)
RR (95% CI)[b]	Reference	1.12 (0.90–1.40)
Respiratory/thoracic hospitalizations (total)		
No. of events	152	72
Event rate per 100 person-years (95% CI)	1.2 (1.1–1.4)	4.7 (3.7–5.9)
RR (95% CI)[a]	Reference	3.79 (2.61–5.51)
RR (95% CI)[b]	Reference	2.48 (1.72–3.56)
Cancer hospitalizations (total)		
No. of events	153	26
Event rate per 100 person-years (95% CI)	1.2 (1.1–1.5)	1.7 (1.2–2.5)
RR (95% CI)[a]	Reference	1.35 (0.88–2.08)
RR (95% CI)[b]	Reference	1.18 (0.75–1.86)
All-cause hospitalizations (total)		
No. of events	3992	717
Event rate per 100 person-years (95% CI)	32.4 (31.4–33.4)	46.8 (43.5–50.3)
RR (95% CI)[a]	Reference	1.44 (1.26–1.63)
RR (95% CI)[b]	Reference	1.19 (1.04–1.35)
Death		
Cardiovascular death		
No. of events (%)	405 (7.3)	87 (12.5)
Event rate per 100 person-years (95% CI)	3.3 (3.0–3.6)	5.7 (4.6–7.0)
HR (95% CI)[a]	Reference	1.71 (1.36–2.16)
HR (95% CI)[b]	Reference	1.35 (1.05–1.73)
All-cause death		
No. of events (%)	875 (15.7)	148 (21.3)
Event rate per 100 person-years (95% CI)	7.1 (6.6–7.6)	9.6 (8.2–11.3)
HR (95% CI)[a]	Reference	1.35 (1.13–1.60)
HR (95% CI)[b]	Reference	1.14 (0.95–1.37)
Composite death/hospitalization outcomes		
All-cause deaths and all-cause hospitalizations (total)		
No. of events	4822	860
Event rate per 100 person-years (95% CI)	39.1 (38.0–40.2)	55.9 (52.3–59.8)
RR (95% CI)[a]	Reference	1.42 (1.26–1.60)
RR (95% CI)[b]	Reference	1.18 (1.04–1.33)

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HF, heart failure; HR, hazard ratio; RR, rate ratio.

[a]Stratified by type 2 diabetes status and adjusted for treatment assignment.

[b]Stratified by type 2 diabetes status and adjusted for treatment assignment, age, sex, geographical region, systolic blood pressure, heart rate, body mass index, log of N-terminal pro-B-type natriuretic peptide, estimated glomerular filtration rate, HF duration, a history of HF hospitalization, left ventricular ejection fraction, New York Heart Association, any coronary artery disease, atrial fibrillation/flutter, and smoking status.

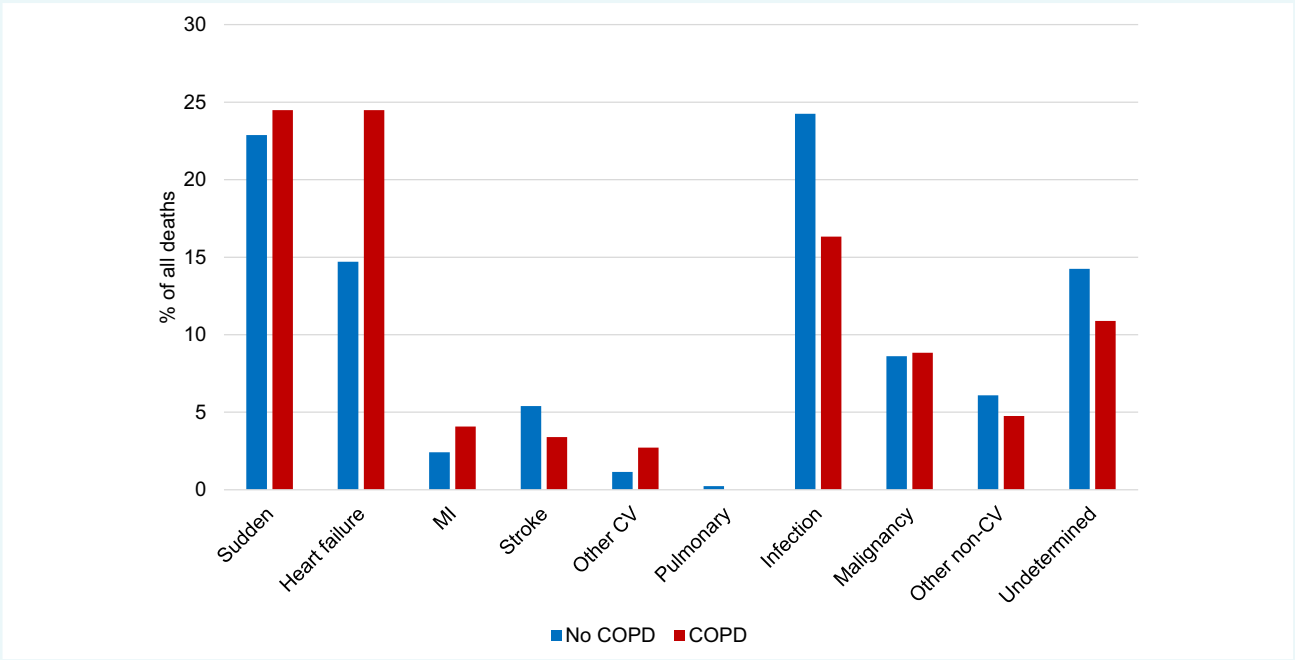


Figure 1 Adjudicated causes of death according to a history of chronic obstructive pulmonary disease (COPD). CV, cardiovascular; MI, myocardial infarction.

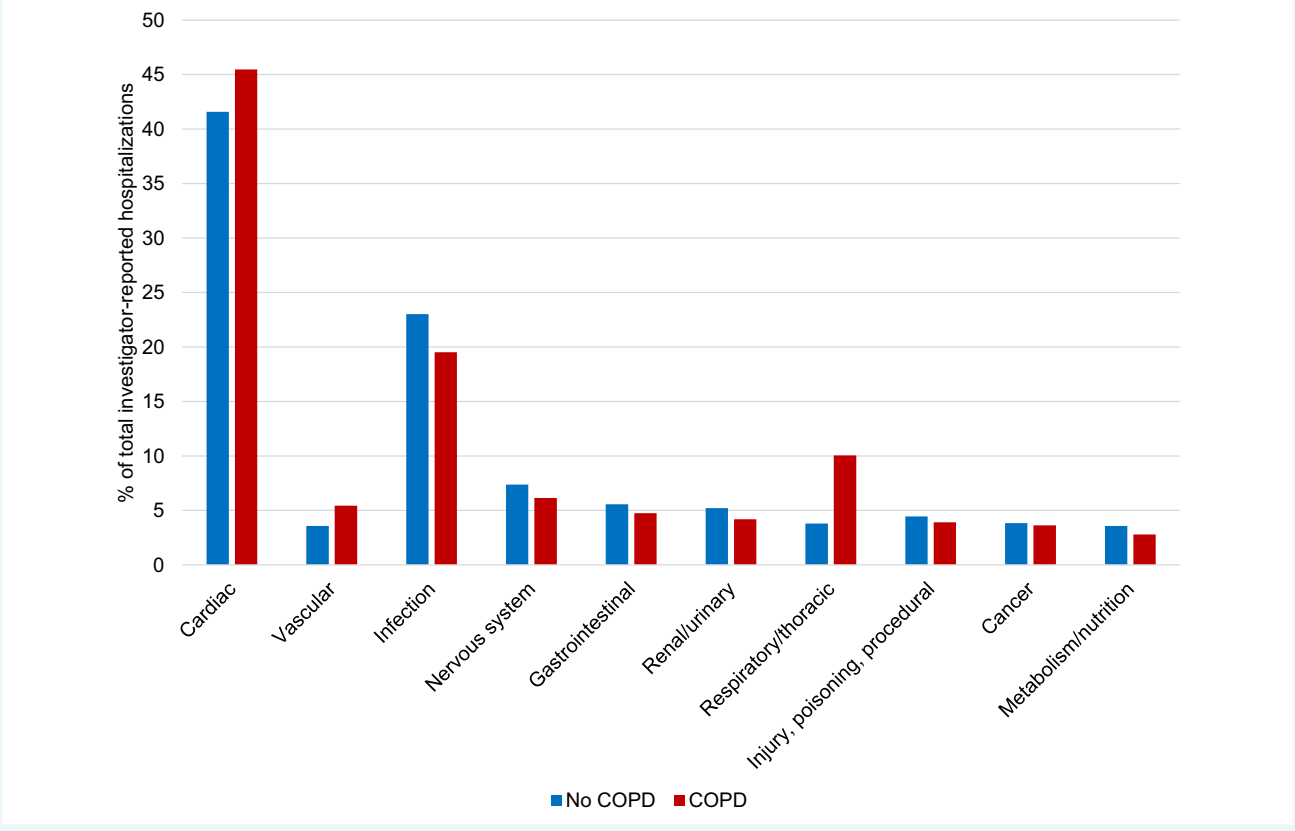


Figure 2 Investigator-reported causes of hospitalizations according to a history of chronic obstructive pulmonary disease (COPD). Investigator-reported reasons for hospitalization were classified according to Medical Dictionary for Regulatory Activities (MedDRA) system organ classes terms. Select hospitalizations had more than one reported cause underlying hospitalization.

was 55.9 (52.3–59.8) among participants with COPD versus 39.1 (38.0–40.2) per 100 person-years in those with COPD (*Table 2*).

Efficacy and safety of dapagliflozin according to a history of COPD

Dapagliflozin, compared with placebo, reduced the risk of worsening HF or cardiovascular death to the same extent in patients with (HR 0.82 [95% CI 0.62–1.10]) and without (0.82 [0.72–0.93]) COPD, with no interaction between COPD and the effect of treatment ($p_{interaction} = 0.98$) (*Table 3*, *Figure 3*). The effect of dapagliflozin was also consistent for all the other clinical outcomes examined regardless of a history of COPD (*Table 3*). Notably, the RR for the composite of all-cause deaths and total all-cause hospitalizations was 0.90 (95% CI, 0.82–0.98) in participants without COPD and 0.91 (0.73–1.14) in patients with COPD ($p_{interaction} = 0.83$; *Table 3*).

Because the absolute risk of clinical outcomes was higher in patients with COPD, the absolute benefit was also greatest in these patients. Assuming a constant treatment effect size in each subgroup, the number of patients needed to treat (NNT) with dapagliflozin over the trial duration to prevent one individual from experiencing the primary endpoint was 19 (95% CI 13–43) for patients with COPD and 30 (95% CI 20–68) for patients without COPD.

The mean increase in KCCQ scores from baseline to 8 months was greater with dapagliflozin compared with placebo in both patients with and without COPD ($p_{interaction} \geq 0.63$; *Table 3* and online supplementary *Table S2*).

The proportions of patients who discontinued trial treatment or experienced serious adverse events was not different between dapagliflozin and placebo among patients with and without COPD (*Table 4*).

In a sensitivity analysis, the definition of COPD was expanded to include asthma. A total of 993 patients (15.9%) had a history of COPD and/or asthma at baseline (i.e. 603 patients had a history of COPD, but not asthma; 299 patients had a history of asthma, but not COPD; 91 patients had a history of both COPD and asthma). Data on outcomes according to a history of COPD and/or asthma are shown in online supplementary *Table S3*, and data on the effects of dapagliflozin, compared with placebo, on clinical outcomes and adverse events, are presented in online supplementary *Tables S4 and S5*, respectively. These analyses yielded similar findings.

In another sensitivity analysis, the effect of dapagliflozin, compared with placebo, on outcomes was examined in the following groups: no history of COPD ($n = 5567$); a history of COPD and no treatment with an inhaled corticosteroid, beta-2-adrenoreceptor agonist, or muscarinic antagonist ($n = 381$); a history of COPD and treatment with either an inhaled corticosteroid, beta-2-adrenoreceptor agonist, or muscarinic antagonist ($n = 313$). The effect of dapagliflozin was consistent across these groups (online supplementary *Table S6*).

Discussion

In this pre-specified analysis of DELIVER, a history of mild-to-moderate COPD was associated with greater impairment of health status and worse clinical outcomes. Dapagliflozin, compared with placebo, reduced the risk of cardiovascular death or worsening HF events (and deaths and hospital admissions from any cause), and improved symptoms and health-related quality of life, to a similar extent in patients with and without mild-to-moderate COPD. In addition, dapagliflozin was safe and well-tolerated, irrespective of COPD status (*Graphical Abstract*).

Patient characteristics according to a history of COPD at baseline

The proportion of patients with an investigator-reported history of COPD in DELIVER was similar to that reported in other HFpEF trials,[1,11–13] but less than in most epidemiological and registry-based studies.[4–6,14,15] One reason for this difference could be the exclusion of patients with severe COPD – a criterion that has been applied in recent HFpEF trials to avoid including participants with COPD misdiagnosed as HFpEF.[16,17] Another reason is likely to be the lack of systematic pulmonary function testing. Unfortunately, spirometry and other pulmonary function tests are underutilized in patients with HF, although even if done, the interpretation of the results of these tests can be difficult in patients with HF (i.e. left-sided decompensation and fluid overload reduce forced vital capacity and forced expiratory volume in 1 s, which can lead to misdiagnosis if spirometry is performed in close proximity to such episodes).[18]

In the present analysis, there were substantial differences in the clinical profile between HFpEF patients with and without COPD, most of which confirmed prior findings.[1,2] Indeed, patients with COPD were older, more often men, and more likely to be current smokers, and they had a greater symptom burden and worse physical function and health-related quality of life. The latter differences are interesting as other measures of HF severity such as LVEF and NT-proBNP levels did not differ substantially between patients with and without COPD. It is possible that symptoms due to COPD causing functional limitation, particularly dyspnoea, may have contributed to the worse NYHA class and KCCQ scores observed in patients with concomitant COPD. Unfortunately, current smoking remained common in patients with COPD (approximately 18%), emphasizing the need to intensify efforts to aid smoking cessation in these patients. The relatively low use of long-acting beta-2-adrenoreceptor agonists and muscarinic antagonists in patients with COPD is also of concern, since both drug classes individually, and in combination synergistically, improve lung function and health status and reduce dyspnoea and exacerbations.[19]

While prior reports have demonstrated a lower use of beta-blockers in patients with COPD compared with those without,[1–3] we found a similar proportion in the two groups. A possible explanation for this discrepancy is that patients with COPD, compared with those without, had a higher prevalence of atrial fibrillation/flutter in DELIVER, but not in other HFpEF trials, and ventricular rate control in atrial fibrillation/flutter is often managed with beta-blockade. However, the use of beta-blockers in patients with COPD is of concern, since the randomized Beta-Blockers for the Prevention of Acute Exacerbations of

Table 3 Effects of dapagliflozin compared with placebo on outcomes according to a history of chronic obstructive pulmonary disease

	No COPD ($n = 5567$)		COPD ($n = 694$)		*p*-value for interaction
	Placebo ($n = 2789$)	Dapagliflozin ($n = 2778$)	Placebo ($n = 342$)	Dapagliflozin ($n = 352$)	
Primary and secondary endpoints					
Primary composite outcome					0.98
No. of events (%)	509 (18.3)	427 (15.4)	100 (29.2)	85 (24.1)	
Event rate per 100 person-years (95% CI)	9.0 (8.2–9.8)	7.3 (6.7–8.1)	14.7 (12.0–17.8)	12.1 (9.8–14.9)	
HR (95% CI)[a]	0.82 (0.72–0.93)		0.82 (0.62–1.10)		
Cardiovascular deaths and worsening HF events (total)					0.70
No. of events	885	674	171	141	
Event rate per 100 person-years (95% CI)	14.4 (13.5–15.4)	11.0 (10.1–11.8)	22.4 (19.3–26.0)	18.4 (15.6–21.7)	
RR (95% CI)[a]	0.76 (0.65–0.89)		0.82 (0.57–1.17)		
Hospitalizations					
HF hospitalizations (total)					0.90
No. of events	587	419	120	89	
Event rate per 100 person-years (95% CI)	9.6 (8.8–10.4)	6.8 (6.2–7.5)	15.7 (13.1–18.8)	11.6 (9.4–14.3)	
RR (95% CI)[a]	0.71 (0.59–0.86)		0.73 (0.47–1.13)		
Cardiovascular hospitalizations (total)					0.69
No. of events	899	761	181	145	
Event rate per 100 person-years (95% CI)	14.6 (13.7–15.6)	12.4 (11.5–13.3)	23.7 (20.5–27.4)	18.8 (16.0–22.2)	
RR (95% CI)[a]	0.85 (0.73–0.97)		0.78 (0.56–1.10)		
All-cause hospitalizations (total)					0.96
No. of events	2109	1883	375	342	
Event rate per 100 person-years (95% CI)	34.3 (32.8–35.8)	30.6 (29.2–32.0)	49.1 (44.4 (54.3)	44.4 (40.0–49.4)	
RR (95% CI)[a]	0.89 (0.81–0.98)		0.89 (0.71–1.13)		
Death					
Cardiovascular death					0.35
No. of events (%)	219 (7.9)	186 (6.7)	42 (12.3)	45 (12.8)	
Event rate per 100 person-years (95% CI)	3.6 (3.1–4.1)	3.0 (2.6–3.5)	5.5 (4.1–7.4)	5.8 (4.4–7.8)	
HR (95% CI)[a]	0.85 (0.70–1.03)		1.06 (0.70–1.61)		
All-cause death					0.59
No. of events (%)	453 (16.2)	422 (15.2)	73 (21.3)	75 (21.3)	
Event rate per 100 person-years (95% CI)	7.4 (6.7–8.1)	6.8 (6.2–7.5)	9.5 (7.6–12.0)	9.7 (7.8–12.2)	
HR (95% CI)[a]	0.93 (0.81–1.06)		1.02 (0.74–1.41)		
Composite death/hospitalization outcomes					
All-cause deaths and all-cause hospitalizations (total)					0.83
No. of events	2543	2279	446	414	
Event rate per 100 person-years (95% CI)	41.3 (39.7–42.9)	37.0 (35.5–38.5)	58.1 (53.0–63.8)	53.7 (48.8–59.1)	
RR (95% CI)[a]	0.90 (0.82–0.98)		0.91 (0.73–1.14)		
Patient-reported outcomes					
KCCQ-TSS					0.78
Change from baseline to 8 months (95% CI)[b]	5.5 (4.8–6.3)	7.9 (7.1–8.6)	5.9 (3.6–8.1)	8.4 (6.2–10.7)	
Placebo-corrected change at 8 months (95% CI)[b]	2.3 (1.3–3.4)		2.6 (−0.6 to 5.8)		

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; RR, rate ratio.

[a]Stratified type 2 by diabetes status.

[b]Mixed-effect models for repeated measurements adjusted for baseline value, visit (months 1, 4, and 8), randomized treatment, and interaction of treatment and visit.

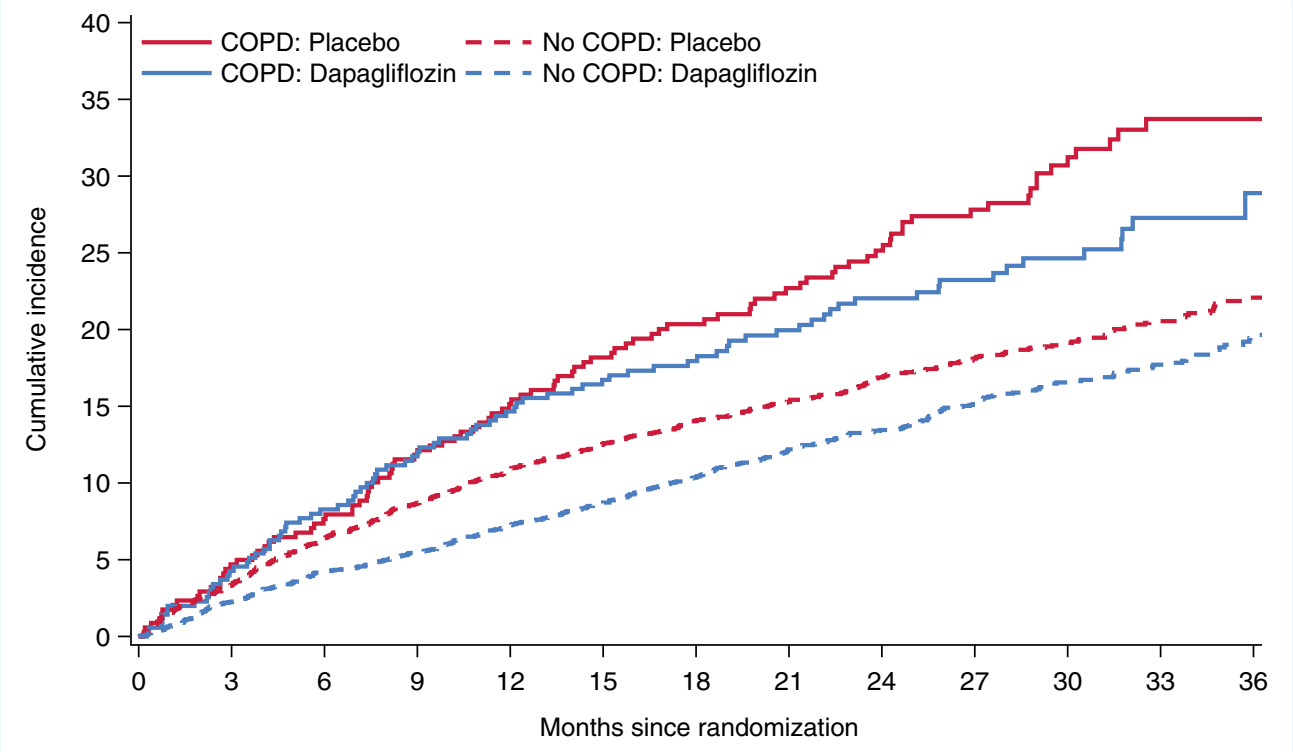


Figure 3 The primary endpoint (time-to-first worsening heart failure event or cardiovascular death) in patients randomized to dapagliflozin or placebo, according to a history of chronic obstructive pulmonary disease (COPD).

Table 4 Adverse events of dapagliflozin compared with placebo according to a history of chronic obstructive pulmonary disease

Adverse event	No COPD ($n = 5557$)		COPD ($n = 694$)		*p*-value for interaction
	Placebo ($n = 2784$)	Dapagliflozin ($n = 2773$)	Placebo ($n = 342$)	Dapagliflozin ($n = 352$)	
Discontinuation of study drug for any reason, *n* (%)	395 (14.2)	383 (13.8)	46 (13.5)	61 (17.3)	0.14
Discontinuation of study drug due to adverse event, *n* (%)	163 (5.9)	160 (5.8)	17 (5.0)	23 (6.5)	0.38
Volume depletion, *n* (%)[a]	29 (1.0)	40 (1.4)	8 (2.3)	9 (2.6)	0.67
Renal adverse event, *n* (%)[b]	80 (2.9)	71 (2.6)	11 (3.2)	13 (3.7)	0.56
Amputation, *n* (%)	24 (0.9)	17 (0.6)	2 (0.6)	2 (0.6)	0.77
Major hypoglycaemia, *n* (%)	6 (0.2)	7 (0.3)	1 (0.3)	1 (0.3)	0.90
Diabetic ketoacidosis, *n* (%)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	N/A

A total of 10 randomized patients were excluded from the safety analysis, as these were performed in patients who had undergone randomization and received at least one dose of dapagliflozin or placebo.
COPD, chronic obstructive pulmonary disease; N/A, not applicable.
[a]Any serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo that was suggestive of volume depletion.
[b]Any renal serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo.

Chronic Obstructive Pulmonary Disease (BLOCK COPD) trial showed that metoprolol exacerbated dyspnoea and increased the risk of severe exacerbations in patients with COPD.[20] However, patients at high risk of exacerbations were enrolled in BLOCK COPD, and the effect of beta-blockers in patients with less severe COPD has not been established.[20] Since beta-blockers are not indicated in HFpEF *per se*, it is advisable to use these drugs only where there are no other options, especially as other concerns have been raised recently about beta-blockers in HFpEF for example, exacerbation of chronotropic incompetence and

possibly (and paradoxically) incident atrial fibrillation.[21,22] Alternative treatment options for the management of atrial fibrillation and hypertension exist and should be considered in patients with HFpEF and concomitant COPD.[1]

Clinical outcomes according to a history of COPD at baseline

In keeping with previous reports,[1–3] we found that a history of COPD was associated with a significantly higher risk of worsening HF events and cardiovascular death in the largest and broadest HFmrEF/HFpEF trial to date, and these associations persisted after comprehensive adjustment for potential confounders, including NT-proBNP and other comorbid conditions.

As expected, the largest single category of death was cardiovascular, and sudden death was the most common mode of cardiovascular death, and our finding of a similar proportion of sudden deaths in patients with and without COPD is in line with previous data.[3] Conversely, the proportion of deaths attributed to worsening HF, the second most common mode of cardiovascular death, was substantially higher in patients with COPD compared to patients without. The next most common cause of death was infection and somewhat surprisingly, this category was less common in patients with COPD compared to those without. As a result, the higher overall rate of death in patients with COPD and HF was driven by an excess of deaths due to worsening HF.

As was the case with death, the two main reasons for hospitalizations were cardiovascular (mainly cardiac) and infectious conditions, accounting for 46% and 23% of all hospitalizations, respectively. Regarding infection-related hospitalizations, a similar puzzling pattern to that seen for causes of death was observed, that is, the proportion of hospitalizations for infectious conditions was slightly higher in patients without COPD than those with COPD, although, as expected, the crude rate of hospitalizations for infectious conditions was numerically higher in patients with COPD. The proportion of hospitalizations for respiratory/thoracic reasons (i.e. including exacerbations of COPD) was very small (~5%) in comparison to cardiac and infectious causes, although was more than two-fold higher in patients with COPD compared to those without.

The proportion of other causes of hospitalizations, including for cancer, was similar in patients with and without COPD. So, as with death, the higher overall rate of hospitalization in patients with COPD was driven mainly by an excess of admissions for cardiac reasons.

Effects of dapagliflozin according to a history of COPD at baseline

In individuals with HF and reduced ejection fraction, COPD does not appear to modify the beneficial effects of guideline-recommended therapies.[18,23–25] However, the effectiveness of certain therapies may be modified by COPD in patients with HFpEF. In the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) (Americas only), the effect of spironolactone, compared with placebo, on cardiovascular and all-cause mortality was modified by a history of pulmonary disease (COPD and/or asthma), such that the risk reduction with spironolactone was greater among those with pulmonary disease.[2] In contrast, a history of COPD did not modify the effect of sacubitril/valsartan, compared with valsartan, on clinical outcomes in the Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON-HF) trial.[1]

In the present analysis of DELIVER, we demonstrated that the efficacy of dapagliflozin on a range of clinical outcomes was not modified by a history of COPD. Specifically, dapagliflozin reduced the risk of time-to-first cardiovascular death or a worsening HF event, as well as cardiovascular deaths and total (first and recurrent) HF events to a similar extent in patients with and without COPD. Because of the predominance of cardiovascular deaths and hospitalizations among overall events in both subgroups of patients, even total all-cause deaths and all-cause hospitalizations were reduced by dapagliflozin. However, because patients with COPD were at higher absolute risk, their absolute benefit was greater, reflected in a smaller NNT for the primary outcome (19 in patients with vs. 30 in those without COPD).

Improvement of health status is a major goal in the management of patients with HF.[14,15] This is even more important in patients with COPD who have a greater symptom burden and worse physical function and health-related quality of life than those without, as confirmed by the NYHA and KCCQ findings in the present study. Although functional limitations due to COPD may have influenced patient answers to the KCCQ, we found that dapagliflozin, compared with placebo, was at least as effective in improving the mean KCCQ scores after 8 months of treatment in patients with COPD as it was in participants without COPD. Symptom control and continuation of daily activities are important for patients with COPD and may help prevent deconditioning and muscle wasting and enhance physical well-being and mental health.[19]

Overall, study drug discontinuation and serious adverse events were generally uncommon with no differences by COPD status. Importantly, study drug discontinuation and serious adverse events were not more frequently reported in the dapagliflozin group than in the placebo group, regardless of COPD status.

Collectively, these data highlight the substantial and clinically meaningful benefits, and favourable safety profile, of dapagliflozin in HFmrEF/HFpEF, irrespective of COPD status and provide further evidence for dapagliflozin as a new treatment option for patients with HF and COPD.

Limitations

The findings of this study should be viewed in the context of potential limitations. Patients enrolled in clinical trials are selected according to specific inclusion and exclusion criteria, and our results may not be generalizable to all patients with HF in the general population, including those with severe COPD. This exclusion criterion may also have influenced the observed associations between COPD status and outcomes, including the lack of

a significantly higher risk of infection-related hospitalizations in patients with COPD compared to those without. Some degree of misclassification of COPD status cannot be precluded as COPD was investigator-reported, and no specific instructions as to how to diagnose COPD were provided in the protocol. We did not have information regarding COPD staging, previous exacerbation history, or use frequency of rescue inhalers. Finally, data on inflammatory biomarkers and echocardiographic measures were not available, although we have previously examined in detail the biomarker and echocardiographic characteristics of patients with HFpEF with and without COPD.[1]

Conclusions

In DELIVER, mild-to-moderate COPD was associated with greater impairment of health status and worse clinical outcomes. Dapagliflozin, compared with placebo, reduced the risk of worsening HF or cardiovascular death, and improved symptoms, physical function, and health-related quality of life, to a similar extent in patients with and without mild-to-moderate COPD. In addition, dapagliflozin was safe and well-tolerated, regardless of COPD status.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References

1. Mooney L, Hawkins NM, Jhund PS, Redfield MM, Vaduganathan M, Desai AS, *et al.* Impact of chronic obstructive pulmonary disease in patients with heart failure with preserved ejection fraction: Insights from PARAGON-HF. *J Am Heart Assoc* 2021;**10**:e021494. https://doi.org/10.1161/JAHA.121.021494
2. Ramalho SHR, Claggett BL, Sweitzer NK, Fang JC, Shah SJ, Anand IS, *et al.* Impact of pulmonary disease on the prognosis in heart failure with preserved ejection fraction: The TOPCAT trial. *Eur J Heart Fail* 2020;**22**:557–559. https://doi.org/10.1002/ejhf.1593
3. Hawkins NM, Wang D, Petrie MC, Pfeffer MA, Swedberg K, Granger CB, *et al.*; CHARM Investigators and Committees. Baseline characteristics and outcomes of patients with heart failure receiving bronchodilators in the CHARM programme. *Eur J Heart Fail* 2010;**12**:557–565. https://doi.org/10.1093/eurjhf/hfq040
4. Cuthbert JJ, Pellicori P, Clark AL. Optimal management of heart failure and chronic obstructive pulmonary disease: Clinical challenges. *Int J Gen Med* 2022;**15**:7961–7975. https://doi.org/10.2147/IJGM.S295467
5. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJV. Heart failure and chronic obstructive pulmonary disease: Diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009;**11**:130–139. https://doi.org/10.1093/eurjhf/hfn013
6. Van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, *et al.* Co-morbidities in patients with heart failure: An analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014;**16**:103–111. https://doi.org/10.1002/ejhf.30
7. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, *et al.*; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;**387**:1089–1098. https://doi.org/10.1056/NEJMoa2206286
8. Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, *et al.* Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: Rationale and design of the DELIVER trial. *Eur J Heart Fail* 2021;**23**:1217–1225. https://doi.org/10.1002/ejhf.2249
9. Solomon SD, Vaduganathan M, Claggett BL, de Boer RA, DeMets D, Hernandez AF, *et al.* Baseline characteristics of patients with HF with mildly reduced and preserved ejection fraction: DELIVER trial. *JACC Heart Fail* 2022;**10**:184–197. https://doi.org/10.1016/j.jchf.2021.11.006

10. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc Ser B Stat Methodol* 2000;**62**:711–730. https://doi.org/10.1111/1467-9868.00259
11. McMurray J, Östergren J, Pfeffer M, Swedberg K, Granger C, Yusuf S, *et al.*; CHARM Committees and Investigators. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: Baseline characteristics of patients in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *Eur J Heart Fail* 2003;**5**:261–270. https://doi.org/10.1016/S1388-9842(03)00052-7
12. McMurray JJV, Carson PE, Komajda M, McKelvie R, Zile MR, Ptaszynska A, *et al.* Heart failure with preserved ejection fraction: Clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. *Eur J Heart Fail* 2008;**10**:149–156. https://doi.org/10.1016/j.ejheart.2007.12.010
13. Shah SJ, Heitner JF, Sweitzer NK, Anand IS, Kim HY, Harty B, *et al.* Baseline characteristics of patients in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial. *Circ Heart Fail* 2013;**6**:184–192. https://doi.org/10.1161/CIRCHEARTFAILURE.112.972794
14. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032. https://doi.org/10.1016/j.cardfail.2022.02.010
15. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
16. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, *et al.*; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;**385**:1451–1461. https://doi.org/10.1056/NEJMoa2107038
17. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, *et al.*; PARAGON-HF Investigators and Committees. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;**381**:1609–1620. https://doi.org/10.1056/NEJMoa1908655
18. Canepa M, Franssen FME, Olschewski H, Lainscak M, Böhm M, Tavazzi L, *et al.* Diagnostic and therapeutic gaps in patients with heart failure and chronic obstructive pulmonary disease. *JACC Heart Fail* 2019;**7**:823–833. https://doi.org/10.1016/j.jchf.2019.05.009
19. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023 Report)*. New York, NY: Elsevier; 2023.
20. Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, *et al.*; BLOCK COPD Trial Group. Metoprolol for the prevention of acute exacerbations of COPD. *N Engl J Med* 2019;**381**:2304–2314. https://doi.org/10.1056/NEJMoa1908142
21. Palau P, Seller J, Domínguez E, Sastre C, Ramón JM, de La Espriella R, *et al.* Effect of β-blocker withdrawal on functional capacity in heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2021;**78**:2042–2056. https://doi.org/10.1016/j.jacc.2021.08.073
22. Habel N, du Fay de Lavallaz J, Infeld M, Koehler JL, Ziegler PD, Lustgarten DL, *et al.* Lower heart rates and beta-blockers are associated with new-onset atrial fibrillation. *Int J Cardiol Cardiovasc Risk Prev* 2023;**17**:200182. https://doi.org/10.1016/j.ijcrp.2023.200182
23. Yeoh SE, Dewan P, Serenelli M, Ferreira JP, Pitt B, Swedberg K, *et al.* Effects of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction patients with chronic obstructive pulmonary disease in EMPHASIS-HF and RALES. *Eur J Heart Fail* 2022;**24**:529–538. https://doi.org/10.1002/ejhf.2350
24. Ehteshami-Afshar S, Mooney L, Dewan P, Desai AS, Lang NN, Lefkowitz MP, *et al.* Clinical characteristics and outcomes of patients with heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: Insights from PARADIGM-HF. *J Am Heart Assoc* 2021;**10**:e019238. https://doi.org/10.1161/JAHA.120.019238
25. Dewan P, Docherty KF, Bengtsson O, de Boer RA, Desai AS, Drozdz J, *et al.* Effects of dapagliflozin in heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: An analysis of DAPA-HF. *Eur J Heart Fail* 2021;**23**:632–643. https://doi.org/10.1002/ejhf.2083